• Letter to the Editor •

Bleb revision and transscleral cyclophotocoagulation for congenital glaucoma patient with Turner syndrome and *DMPK* gene mutation: a case report

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Dear Editor,

We report a case of congenital glaucoma patient with Turner syndrome (TS) and *DMPK* gene mutation whose intraocular pressure (IOP) was controlled by multiple bleb revision with antiproliferation medication followed by transscleral cyclophotocoagulation (TCP).

TS is one of the most common sex chromosome abnormalities with an incidence of 1/2000 to 1/2500 in women[1]. The disease is mainly associated with complete deletion of the X chromosome (45, X) and to a lesser extent karyotypes of chimerism (45, X/46, XX), isobaric chromosomes, ring X chromosomes, and carrying the Y chromosome (45, X/46, XY). The main clinical manifestations include short stature, webbed neck, elbow valgus, hearing loss, delayed puberty, infertility, ovarian insufficiency, low levels of growth hormone, endocrine disorders (hypothyroidism, type 1 and type 2 diabetes, and osteoporosis), and autoimmune disorders (Hashimoto's thyroiditis, celiac disease and inflammatory bowel disease[2]), *etc*. Ocular manifestations of TS include amblyopia, strabismus, hypotony, and hypoacusis (more than 25% of cases). Some patients show ptosis, epicanthus, hypertelorism, antimongoloid, palpebral fissures, red-green deficiency, and nystagmus (5%–25% cases) while rare presentations include early-onset cataracts, congenital glaucoma, and blue sclera[3] (less than 5% cases). *DMPK* gene mutation could induce cataract, ptosis, nystagmus, optic nerve atrophy, and retinitis pigmentosa. To the best of our knowledge, it is the first time we have reported TS syndrome and *DMPK* gene mutation in one patient. This may explain the refractory nature of the ocular disease in this patient with TS associated with glaucoma.

CASE PRESENTATION

Ethical Approval Approval from PUTH Ethics Committee was obtained (approval No.2020-096-03). Written informed consent was obtained from the patient for publication of this Case Report and accompanying images.

A 27-year-old female, 150 cm in height and 60 kg in weight was diagnosed with bilateral congenital glaucoma after birth and underwent trabeculectomy combined with trabeculotomy in both eyes at 10 months old with no significant improvement in vision and a gradual atrophy in the right eye.

Surgical Procedure At the age of 19 (2015), the visual acuity (VA) was 0.8 (logMAR) with 35 mm Hg IOP in her left eye. Flat bleb, clear cornea, and high insertion of iris were found. Bleb revision with 0.2 mL 2.5% 5 fluorouracil (5-FU) subconjunctival injection was performed twice. IOP was controlled among 15–21 mm Hg with 2 antiglaucoma eye drops (0.03% bimatoprost and 0.2% brimonidine tartrate *b.i.d.*) for almost 4y. Four years later (2019), bleb revision with multiple 0.2 mL 2.5% 5-FU subconjunctiva injections were repeated due to IOP raised to 35 mm Hg. Bleb was reconstructed and IOP was controlled under 21 mm Hg with 3 antiglaucoma eye drops (0.03% bimatoprost, 0.2% brimonidine tartrate *b.i.d.* and 0.5% Levobunolol Hydrochloride *b.i.d.*) but the toxic reaction of 5-FU occurred on the cornea and no more 5-FU was injected. One year after that, the IOP increased to 63 mm Hg after she got the flu. She has undergone twice TCP treatments since then. TCP treatment was performed using the Oculight SL/SLX810 G-probe (IRIDEX Corporation, Mountain View, CA, USA). Twenty applications at 2000 mW for 1500ms. The

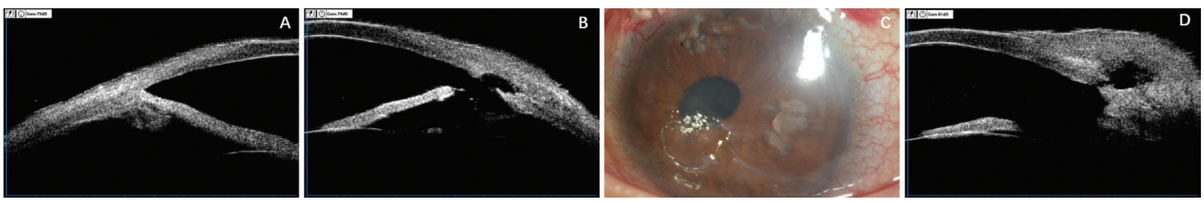

Figure 1 Ocular examination results during treatment A: Ultrasound biomicroscope (UBM) showed anterior chamber angle dysplasia and iris high insertion (2015); B: UBM showed flat bleb and drainage pathway (2015); C: Slit lamp showed clear cornea with central epithelial defect (2019); D: UBM showed enlarged filtering bleb and drainage pathway (2019).

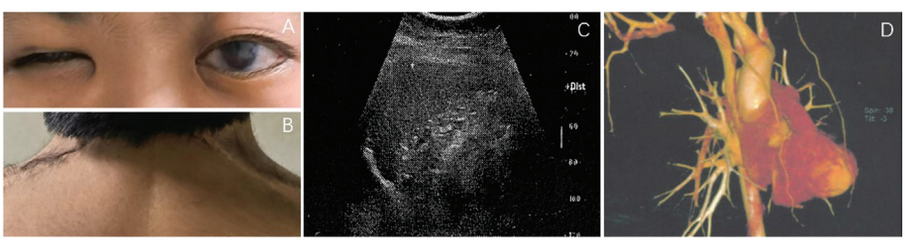

Figure 2 Patient system check results A: Atrophy and ptosis of the right eye; B: Congenital webbed neck removed by plastic surgery; C: B-scan ultrasound showed left renal agenesis; D: CT showed aortic stenosis. CT: Computed tomography.

3- and 9-o'clock positions were spared to avoid the long ciliary nerves and vessels. A total of 300° was treated every time. Nowadays, her VA was 0.9 (logMAR) and IOP maintained around 20 mm Hg with 2 antiglaucoma eye drops (0.2% brimonidine tartrate *b.i.d.* and 0.5% levobunolol hydrochloride *b.i.d.*, Figure 1).

System Check System disorders included hypertension, diabetes, frequent diarrhea, congenital webbed neck redundancy (removed), aortic valve malformation and mild regurgitation (echocardiography), post-catheter type aortic constriction (total aortic CTA), left renal agenesis, left pleural adhesions and congenital uterine agenesis *etc* (Figure 2).

Genetic Testing The whole exome genetic analysis demonstrated a deletion of X chromosome (45, XO) as a whole, and a heterozygous missense mutation in the *DMPK* gene (c.335T>C, p.M112T) on chromosome 19 (Figure 3).

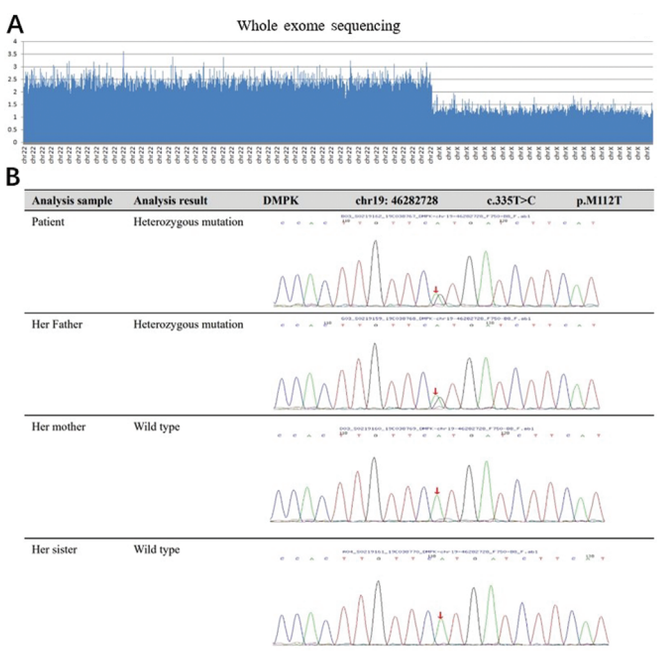

Figure 3 The whole exome genetic analysis demonstrated a deletion of X chromosome (45, X) as a whole, and a heterozygous missense mutation in the *DMPK* gene (c.335T>C, p.M112T) on chromosome 19.

DISCUSSION

Cases of TS with glaucoma are relatively rare (Table 1)[4-6]. The ocular manifestations of our patient were mainly congenital glaucoma with ptosis, amblyopia, blue-violet blindness, and nystagmus. Consistent with the description by Denniston and Butler[3] in patients with TS, our patient was associated with more rare manifestations such as blue-violet blindness, cataract, and dry eye. Previous articles showed trabeculectomy is proposed as a first intervention with a success rate varies from 54% to 90% and the risk of postoperative complications is comparable to other techniques[7]. The IOP of our patient was under controlled almost 19y after filtering surgery and subsequently treated with multiple bleb revisions with antiproliferative medications that could maintain a stable condition for several years. Later, due to the accumulated toxic effects of 5-FU, further injections were not recommended. To rescue the patient's only eye, twice TCP and anti-glaucoma eye drops are used to control the IOP of the left eye.

TCP is effective in all types of refractory glaucoma and is usually used when other procedures have failed or are not indicated. The cumulative success rate of TCP was almost 94% 1y postoperatively[8] and repeat treatments are usually required to achieve better IOP control. When the patient's corneal condition was not suitable to receive more antiproliferative medication, TCP was selected to control the IOP. There are few previous articles that study TCP on glaucoma patients with TS. This case showed TCP was an effective treatment for such

Table 1 Previous researches about ocular manifestations with Turner's syndrome

Year/author/No.	Age/sex	Diagnostic results	First symptoms	System anomaly	Eye abnormalities	Karyotype	Treatment	Prognosis
1967/Khodadoust A, *et al*[4]/1	13y/M	Retinal detachment OD Intumescent cataract with secondary glaucoma OS	Blindness OS; gradual loss of vision OD	Pterygium coli low-set ears high-arched palate partial ptosis low nuchal hairline mild degree of hyperTelorism short stature cryptorchism	OD: FC/17 mm Hg OS: LP/35 mm Hg Shallow anterior chamber peripheral atrophy of the iris advanced intumescent cataract retinal detachment secondary glaucoma	Normal chromosome karyogram adequate number of chromosomes	Retinal detachment Procedure Franceschetti iridectomy, aspiration of cataract OS	OS: 20/200 IOP: normal OU Long-standing retinal detachment
1997/Lloyd IC, *et al*[5]/3	2mo/F	TS syndrome combined with congenital glaucoma	Tearing and photophobia	N/A	OS: High IOP Cloudy cornea edematous with splits in Descemet's membrane trabeculodysgenesis OU: iris hypoplasia	45, X/46, X, idic(Y)	Nasal goniotomy temporal goniotomy	IOP remained controlled, cornea cleared
	5mo/F	TS syndrome combined with congenital glaucoma	Watering eyes and photophobia	Streak gonads	OD 24 mm Hg OS 20 mm Hg OU: corneal edema, splits in Descemet's membrane	45, X/46, X, idic(Y)	inferior goniotomy OD upper temporal quadrant trabeculotomy, and nasal goniotomy OS	OD: 6/9, OS: 6/12 IOP: remained controlled Photophobia, low hypermetropic refractive error
	Newborn/F	TS syndrome combined with congenital glaucoma	Congenital imperforate anus	Developmental delay	OD: 20 mm Hg OS: 21 mm Hg Cloudy corneas OU: Descemet's membrane splits	45, X/47, XXX	trabeculotomy and inferior goniotomies OU	OD: 10 mm Hg OS: 9 mm Hg Deeply cupped optic discs mild developmental delay
2005/Rao VA, *et al*[6]/1	22y/F	Goldenhar syndrome combined with juvenile glaucoma	Loss of vision OS	Epibulbar dermoid preauricular appendages uterine right renal agenesis	OD: 6/9, 30 mm Hg Cup-disc ratio of 0.5 OS: NLP/50 mm Hg Relative afferent pupillary defect OU: glaucomatous optic atrophy Goldmann mirror revealed Grade IV angle	46 XX, 45 XO	Topical 0.5% timolol maleate, 2% Pilocarpine nitrate preparations, trabeculectomy with mitomycin C	IOP reduced, OD: 13 mm Hg

N/A: Not available; OD: Right eye; OS: Left eye; OU: Both eyes; FC: Finger counting; LP: Light perception; NLP: No light perception.

patients, suggesting that TCP treatment may be innovatively applied to such patients.

Glaucoma drainage device are another option for advanced refractory cases of congenital glaucoma. Previous studies have shown that mean IOP decreased substantially after glaucoma drainage devices implantation for at least 24mo and the proportion of eyes meeting the criteria for success was 87% and 77% at 12 and 24mo postoperative respectively[9] which can be an alternative surgical option. This patient is young with significant proliferation and conjunctival scarring so drainage valve implantation may be our last choice.

Previous research showed that antimetabolites can be used after Ahmed glaucoma valve failure[9], and 5-FU injection as an effective and safe procedure after trabeculectomy failure[10]. The reason why she has very severe corneal toxic effects is probably related to her gene mutation. TS patients usually have ovarian insufficiency and dry eye is more common in women with ovarian insufficiency than in women with normal ovarian function and is mediated by sex hormone receptors on the ocular surface[10]. Dry eye may exacerbate the toxic effects of 5-FU of cornea and increase the refractoriness of this case.

The reason why the IOP of the patient is so hard to control is probably related to her gene mutation. There are two kinds of gene mutation in this patient. Except for TS mentioned above, *DMPK* gene heterozygous missense mutation was also confirmed. The *DMPK* gene encodes a serine/threonine kinase with substrates including myostatin, the β-subunit of the L-type calcium channel, and phosphoproteins, and its action is closely related to the Rho family. Rho kinase, a key enzyme involved in cellular signaling pathways, plays a crucial role in regulating cell morphology and permeability. Considering its impact on the cytoskeleton of trabecular meshwork (TM) cells and Schlemm's canal cells[11], a genetic mutation associated with Rho kinase may potentially complicate the treatment of glaucoma. Ocular problems include cataract, ptosis, nystagmus, optic nerve atrophy and retinitis pigmentosa[11]. TS and *DMPK* gene mutation both could induce glaucoma, cataract, nystagmus and ptosis. Nystagmus and ptosis may affect the accuracy of eye examination, increase the difficulty of surgery and subsequently affect the prognosis of glaucoma treatment.

CONCLUSION

In summary, we report a patient of congenital glaucoma with TS and *DMPK* gene mutation which may caused refractory glaucoma. The patient's VA and IOP were maintained by multiple bleb revision and TCP with antiglaucoma medication. The limitation of this study is only one patient was reported and the mechanism of how deletion of X chromosome (45, XO) and *DMPK* gene mutation affect drainage function is not clear. Further investigation of the mechanism of multiple gene

mutation in congenital glaucoma was needed to find a new treatment.

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